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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,113	08/21/2001	Clague P. Hodgson	518.001US2	8040

21186 7590 04/21/2004

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,113	HODGSON, CLAGUE P.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9-22-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-87* is/are pending in the application.

4a) Of the above claim(s) *86 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/21/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 77-87 remain pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 77-85, in the response filed 9-22-03 is acknowledged.

Claims 86 and 87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed 9-22-03.

Claims 77-85 are under consideration in the instant office action.

Priority

The first line of the specification was amended on 1-21-03 to reflect this application is a CON of 08/622,336 filed Nov. 9, 1995, the national stage of PCT/US94/02752 filed March 14, 1994, a CIP of 08/194,208, a CIP of 08/130,638, a CIP of 08/097,721, a CIP of 08/060,568, and a CIP of 08/030,766.

The status of 08/622,336 must be updated to reflect that 08/622,336 is now US Patent 6,287,863.

The status of 08/030766, as being abandoned, must be updated in the first line of the specification.

Information Disclosure Statement

The IDS filed 8-21-01 has been considered. See attached copy.

Specification

The abstract filed 8-21-01 is acceptable.

The descriptions of Fig. 4 and 5 on pg 13, line 27, should be separated in different paragraphs.

The descriptions of Fig. 7 and 8 on pg 14, line 2, should be separated in different paragraphs.

The description of Fig. 7 should begin Fig. 7A-7D.

The description of Fig. 8 should begin Fig. 8A-8D.

The status of the application on pg 3, line 27, and pg 43, line 29, should be updated. Please review the specification for other application numbers.

Claim Objections

Use of the term "which" throughout the claims is grammatically incorrect as written. Please replace "which" with –that--.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support for the new claims filed in the preliminary amendment filed 8-21-01 was provided and none can be found. Therefore, the claims are rejected under new matter. The new phrases are as follows:

"expressing a DNA sequence into an animal" (77, 80),

"from step (d)(1)" (77, 80-82, 84, 85),

"introducing the transformed donor cell to an organ of an animal, tissue of an animal, an embryo of an animal or an animal" (77, 80, 82),

"identifying a transformed cell which contains the DNA sequence of (a)(vi)" (77, 80, 85).

"wherein the donor cell is... ... or an embryo" (78),

"capable of packaging nucleic acid molecules into a virion to yield a transformed donor cell" (80),

"producing a double-stranded cDNA containing a gene which is capable of homologous recombination with the genome of a cell" (81),

"inserted into the vector 3' of the transcription initiation site... ...with the genome of the cell" (81),

"identifying a cell which contains an integrated form of the vector... ...which is capable of homologous recombination with the genome of the cell",

"reconstituting tissues with genetically modified embryonic stem cells" (82),

"where the embryonic stem cell has been modified with respect to the histocompatibility antigens present on the stem cell surface" (83),

"preparing genetically modified ES cells" (84), and

"autonomously replicating DNA sequences to the genome of a recipient cell" (85).

Claims 77-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing a vector into a packaging cell *in vitro,* wherein said vector comprises (i)-(v) and (vii) of claim 77, step a) (without the phrase ("from step (d)(1)") and a nucleic acid sequence encoding a protein, introducing a viral particle made by the packaging cell into a cell *in vitro*, and expressing the protein in the cell, does not reasonably provide enablement for using the method to make transgenic animals other than mice and chickens, for using the method in gene therapy or for using the method to transduce any ES cell other than mouse ES cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 78, 82, 83, 84 specifically require embryonic stem cells. However, the state of the art at the time of filing was that ES cells in species other than mice did not exist. While embryonic cells had been isolated in other species, the cells did not proliferate in culture and were not capable of making germ cells upon being introduced into an embryo (Bradley, 1992, Biotechnology, Vol. 10, pg 534-539; sentence bridging pg 537-538; Seamark, 1994, Reproductive Fertility and Devel., Vol. 6, pg 653-657; pg 6, abstract). Simkiss (1994, Maclean ed. Animals with novel genes, Cambridge Univ. Press, Cambridge, England; NY, NY, pg 106-137) specifically taught that an avian stem cell that is pluripotent for the germ-line and capable of being maintained in cell culture

did not exist (pg 120 last sentence of 1st full ¶). Since the effective filing date of applicants invention, Mullins (1996, J. Clin. Invest., Vol. 98, pg 1557-1560) taught that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated" (pg 1158, col. 2, lines 6-10). The specification suggests using the vector to transform cells injected into embryos for the purpose of making transgenics of any species (pg 53, lines 16-22). The specification does not teach how to obtain ES cells in any species. Without such guidance taken with the state of the art, it would have required one of skill undue experimentation to work with ES cells as claimed in any species other than mice. Therefore, the limitation of embryonic stem cells should be limited to mouse embryonic stem cells.

Claims 77, 78 and 80-85 require introducing a donor cell into an embryo and detecting the vector in an organ, tissue, embryo or animal. The only purpose for such a method is to make transgenics.

However, the state of the art at the time of filing was that introducing transfected cells into embryos to make transgenics had only been successfully performed in mice using ES cells and chickens using PGCs. Transgenic mice are discussed above. In chickens, stage XI PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick et al., Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Thus, it was unpredictable how to make transgenics mice without ES cells

or transgenic chickens without PGCs. It was also unpredictable how to make transgenics in species other than mice and chickens. Applicants have provided any enabled use for introducing transfected cells into embryos other than to make transgenics. Applicants have not provided any guidance or discussion regarding how to make or isolate cells capable of germline transmission upon being implanted into an embryo. The specification does not discuss the essential features of ES cells or PGCs so that other mouse or chicken cells could be used to make transgenics. The specification does not discuss the essential features of ES cells or PGCs so that cells capable of germline transmission could be found in other species. Thus, one of skill would rely on the mouse ES cells and chicken PGCs known in the art. Therefore, transfected cells introduced into an embryo should be limited to mouse ES cells or chicken PGCs.

Claims 77-85 require introducing a vector or cell comprising a vector into an "organ of an animal, tissue of animal... ...or an animal". The only purpose disclosed for such a method is for treatment, i.e. gene therapy. Claim 82 specifically is directed towards "reconstituting tissues with genetically modified ES cells." However, the specification does not enable one of skill to introduce a retroviral vector or cell comprising a retroviral vector into an animal such that a therapeutic effect occurs.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995,

FASEB J., Vol. 9, pg 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Crystal (1995, Science, Vol. 270, pg 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409). Therefore, the state of the art was that the parameters required to obtain a therapeutic effect were unpredictable.

Since the time of filing, the art of gene therapy continued to be unpredictable. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) taught that the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" prevented obtaining a therapeutic effect using gene therapy (pg 53, 1st ¶). Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviewed retroviral vectors known in the art for use in gene therapy and discussed problems associated with them. Verma taught that in 1997, vector targeting to the tissue required to obtain the desired effect had not yet been achieved (see entire article).

The specification merely provides generic teachings and statements regarding gene therapy and treatment using a retrovirus. For example the paragraph bridging pg 47-48 discusses reconstituting an animal with hematopoietic stem cells expressing growth factors to treat disease. However, the specification does not teach the growth

factor or amount of growth factor required to treat any disease or how to obtain adequate expression of a growth factor in vivo using the vector of the invention so that therapeutic levels of expression occur in the desired tissue. The specification does not teach the specific combination of elements required to overcome the unpredictabililty in the art by teaching the specific combination of elements required to obtain a therapeutic effect using a retrovirus as claimed. I.e. the specification does not teach the specific combination of promoter, protein, tissue of interest, amount of expression and route of administration required to introduce a retrovirus into a tissue or organ of animal or anywhere into an animal as claimed such that a therapeutic effect would occur. Based on the unpredictability in the art taken with the dearth of information in the specification, it would require one of skill undue experimentation to determine the combination of elements required to obtain such an effect using a retrovirus as claimed. Therefore, claims relating to introducing a retrovirus or cells transduced with a retrovirus into a tissue or organ of an animal

Claim 80 encompasses introducing a vector into a packaging cell and introducing the packaging cell into an embryo. The specification does not provide a use for such a method. It is assumed, therefore, that the method would be used for making transgenics and is rejected for reasons above regarding transgenics.

Claim 80 encompasses introducing a vector into a packaging cell and introducing the packaging cell into an organ of an animal, a tissue of an animal or an animal. The specification does not provide a use for such a method. It is assumed, therefore, that

the method would be used for gene therapy and is rejected for reasons above regarding gene therapy.

Claim 81 requires "producing a double-stranded cDNA containing a gene which is capable of homologous recombination with the genome of a cell" using a retroviral vector with a DNA sequence "inserted into the vector 3' of the transcription initiation site in the 5' LTR of the vector which DNA sequence comprises a polyd(T) tract 3' to an open reading frame which is capable of homologous recombination with the genome of the cell". The specification does not teach such a method (112/1st new matter above) and cannot be found in the art. It is unclear whether such a method is used in making transgenics, gene therapy or both. Therefore, it cannot be determined how to use such a method or whether such a method is enabled. Given the absence of teachings in the specification, it would require one of skill undue experimentation to determine how to introduce a vector into a cell as claimed such that a double-stranded cDNA containing a gene capable of homologous recombination with the genome of a cell was produced.

Claim 85 requires "delivering an autonomously replicating DNA sequences to the genome of a recipient cell". The specification does not teach such a method (112/1st new matter above) and cannot be found in the art. The specification does not teach whether such a method is used in making transgenics, gene therapy or both. The specification does not teach what DNA sequences replicate autonomously while in the genome of a cell. Therefore, it cannot be determined how to deliver such a DNA sequence to the genome of a cell, what DNA sequences replicate autonomously or how to use such a method. Given the absence of teachings in the specification, it would

require one of skill undue experimentation to determine how to deliver an autonomously replicating DNA sequence into the genome of a recipient cell as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 77-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77 and 80 are indefinite because DNA sequences are not expressed "into" an animal (line 1).

Claims 77, 80 and 85 are indefinite because the metes and bounds of "donor cell" are unclear. It is unclear if the cells are limited to packaging cells that are then introduced into "an organ of an animal, tissue of an animal an embryo of an animal or an animal" or if the cells are infected with a virus made by a packaging cell line and the introduced into "an organ of an animal, tissue of an animal an embryo of an animal or an animal." Clarification is required.

The phrase "to yield a transformed donor cell" in step a) of claims 77, 81, 85 is unclear. It is unclear if the phrase is an intended use or if "introducing a DNA transfer vector into a donor cell" results in a transformed donor cell. Replacing "to yield" with "thereby producing" is suggested.

Use of the word "linked" in step a) of claims 77, 80-82, 84, 85 is confusing. It cannot be determined if the word is intended to mean elements i-vii are connected in

the order shown or have some particular structure beyond merely being in the vector. Deletion of the word is suggested, as it does not further limit the structure of the vector.

Claim 77, 80-82, 84 and 85 are indefinite because "from step (d)(1)" ((a)(iv)(2)) does not have antecedent basis.

The phrase "introducing the transformed donor cell to" is confusing (claim 77, 80, 82, step b)). Cells are not introduced "to" organs, tissue, embryos or animals. Cells are introduced –into-- organs, tissue, embryos or animals. Correction is required.

Claims 77 and 80 are indefinite because step c) is not commensurate in scope with the preamble of the claim. First, while the organ, tissue or embryo may be "of an animal" as in step b), the organ, tissue or embryo may not be in and animal as in the preamble of the claim. Second, the step of identifying cells that express a DNA sequence makes the claim an assay for detecting expression, i.e. whether or not expression occurs, not a method of expressing a DNA sequence as in the preamble. If applicants intend the claim to be a method of expressing a DNA sequence, step b) should clearly result in expressing the DNA sequence of (a)(vi) in a cell.

Claim 78 is indefinite because an embryo is not a cell. Therefore, "embryo" cannot further limit the term "cell."

Claim 80 is indefinite because the phrase "capable of packaging nucleic acid molecules into a virion to yield a transformed donor cell" is confusing. It is unclear if applicants intend the phrase to be a step in the method, i.e. that the DNA transfer vector is packaged into a virion, or merely that the cell is capable of packaging. In this claim, donor cell is especially confusing because the term "packaging cell" seems to be

appropriate in step a) (but has not been used); however, "packaging cells" are not "introduced... ...to an organ of an animal, tissue of an animal, an embryo of an animal or an animal" as in step c).

Claim 81 is indefinite because step b) is not commensurate in scope with the preamble of the claim. The step of identifying cells that express a DNA sequence makes the claim an assay for detecting expression, i.e. whether or not expression occurs, not a method of producing a double stranded cDNA containing a gene as in the preamble. If applicants intend the claim to be a method of producing a double stranded cDNA, step b) should clearly result in producing a double stranded cDNA.

The phrase "which is capable of homologous recombination with the genome of the cell" (claim 81) is unclear. If the cell already "contains an integrated form of the vector" in step (b), has homologous recombination already occurred? It cannot be determined if the phrase is a functional limitation of the vector or if homologous recombination has actually occurred.

The phrase "to yield a transformed embryonic stem cell" in step a) of claims 82 and 84 is unclear. It is unclear if the phrase is an intended use or if "introducing a DNA transfer vector into an embryonic stem cell" actually results in a transformed embryonic stem cell. Replacing "to yield" with "thereby producing" is suggested.

The term "donor cell" in claim 82, step (b) lacks antecedent basis.

Claims 82 and 84 are confusing because a virion must be used to infect embryonic stem cells, not the vector that needs packaging as set forth in step a) i-vii).

Claim 82 is indefinite because step c) is not commensurate in scope with the preamble of the claim. First, while the organ, tissue or embryo may be "of an animal" as in step b), the organ, tissue or embryo may not be in and animal as in the preamble of the claim. Second, the step of identifying cells that express a DNA sequence makes the claim an assay for detecting expression, i.e. whether or not expression occurs, not a method of reconstituting tissues with genetically modified embryonic stem cells as in the preamble. If applicants intend the claim to be a method of reconstituting tissues with genetically modified embryonic stem cells, step b) should clearly set forth that the cells are introduced into an animal and a tissue of the animal is reconstituted with the transformed embryonic stem cell. However...

Claim 82 is indefinite because the metes and bounds of what applicants consider "reconstituted" cannot be determined. It is unclear if the term is limited to "replacing" one tissue with genetically modified ES cells or if the term is intended to mean the tissue comprises genetically modified ES cells.

Claim 83 is indefinite. The structural or functional modification "with respect to the histocompatibility antigens present on the stem cell surface" cannot be envisioned. Has the stem cell been genetically modified to express an antigen or an MHC molecule or exposed to an antigen or MHC molecule. It cannot be determined if the cell has additional proteins or is missing proteins. It cannot be determined if endogenous proteins on the surface have been changed or if they have been deleted. As written, the structure of the modification is not clearly set forth in claim 83.

Claim 84 is indefinite because step b) is not commensurate in scope with the preamble of the claim. The step of identifying cells that comprise a DNA sequence makes the claim an assay for detecting whether or not transformation has occurred, not a method of preparing genetically modified ES cells as in the preamble. If applicants intend the claim to be a method of preparing genetically modified ES cells, step b) should clearly result in obtaining genetically modified ES cells.

The metes and bounds of what applicants consider "autonomously replicating DNA sequences" as in the preamble and step a) (vi) of claim 85. No such sequences can be envisioned. It is also unclear to what the sequence is "autonomous." Can the sequence replicate without a cell?

Use of "recipient cell" in the preamble of claim 85 and "donor cell" in step a) of claim 85 is confusing. It is unclear if the cells are two different types of cells.

Claim 85 is indefinite because step b) is not commensurate in scope with the preamble of the claim. The step of identifying cells that comprise a DNA sequence makes the claim an assay for detecting whether or not transformation has occurred, not a method of "delivering an autonomously replicating DNA sequence to the genome of a recipient cell" as in the preamble. If applicants intend the claim to be a method of "delivering an autonomously replicating DNA sequence to the genome of a recipient cell", step b) should clearly result in a donor cell comprising an autonomously replicating DNA sequence.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 77-85 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,287,863. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass using the same vector.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER